Ring-cleavage of Isoxazoles with Heterocyclic Amines. Synthesis of Fused Pyrimidines

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The reaction between 2-substituted ethyl 2,5-dihydro-5-oxoisoxazole-4-carboxylates (**2a,b**) and heterocyclic amines **1**, **4**, and **6**, having the amino group in position 2 with respect to the nuclear nitrogen afforded fused pyrimidines **3**, **5**, and **7**.

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Although many studies on the ring-cleavage of 2-substituted alkyl 2,5-dihydro-5-oxoisoxazole-4-carboxylates with nucleophiles have been reported in the literature [1], only in few cases these reactions have been employed for the synthesis of heterocyclic compounds [2].

This paper deals with the reaction of 2-substituted ethyl 2,5-dihydro-5-oxoisoxazole-4-carboxylates **2a,b** and heterocyclic amines **1**, **4**, and **6** that led to the formation of fused pyrimidines **3**, **5**, and **7**. A possible reaction pathway is reported in the Scheme.

The reactions were performed very easily by heating the two reactants in the absence of a solvent to give the reaction products in fair yields.

The ir spectra of the reaction products give no useful informations of their structure since they show unstructured bands and only a CO absorption at about 1670 cm^{-1} is detected. The ^1H nmr spectra of the reaction products are in agreement with the assigned structures **3**, **5**, and **7**. In fact a singlet signal at about δ 16 due to an enol type OH proton is detectable. This signal disappears very quickly upon treatment with deuterium oxide. Furthermore a singlet signal at about δ 11.5 due to the proton linked to the

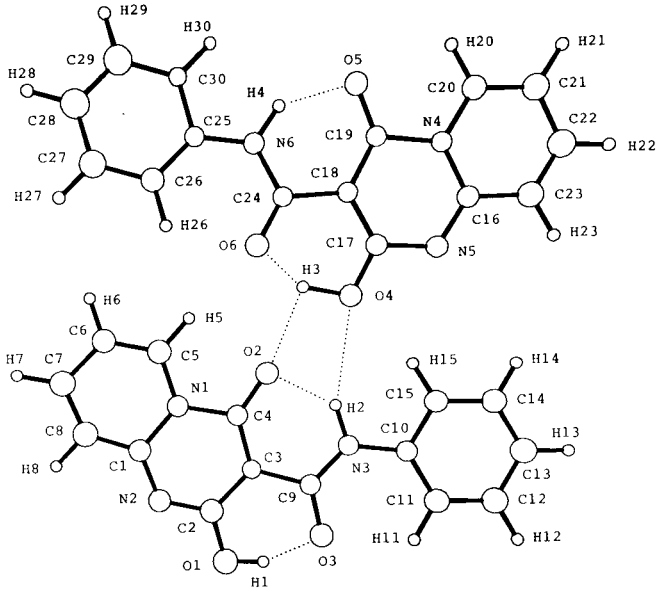

Figure 1. Structure of 3a as determined by X-ray analysis.

Scheme

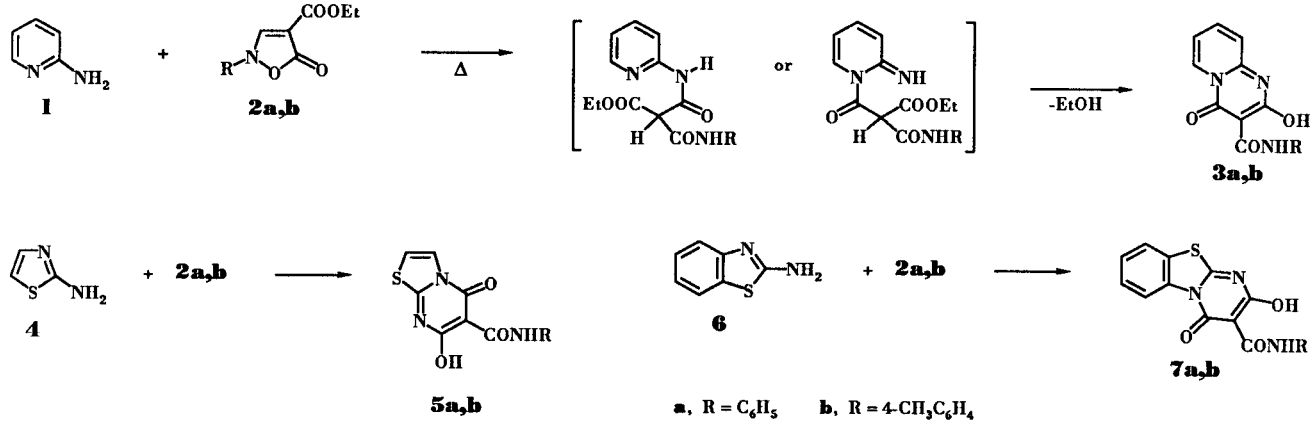

Table 1

Bond Distances (Å) and Angles (°)

Molecule 1		Molcecule 2	
N1 - C1	1.43(2)	N4 - C16	1.38(1)
N1 - C4	1.45(2)	N4 - C19	1.45(1)
N1 - C5	1.39(1)	N4 - C20	1.37(1)
C1 - N2	1.34(2)	C16 - N5	1.33(1)
C1 - C8	1.35(2)	C16 - C23	1.43(2)
N2 - C2	1.30(2)	N5 - C17	1.33(2)
C2 - O1	1.35(2)	C17 - O4	1.34(1)
C2 - C3	1.41(2)	C17 - C18	1.40(2)
O1 - H1	0.98(12)	O4 - H3	1.16(11)
C3 - C4	1.35(2)	C18 - C19	1.38(1)
C3 - C9	1.44(2)	C18 - C24	1.48(2)
C4 - O2	1.25(1)	C19 - O5	1.25(1)
C5 - C6	1.34(2)	C20 - C21	1.37(2)
C6 - C7	1.45(2)	C21 - C22	1.40(2)
C7 - C8	1.33(2)	C22 - C23	1.32(1)
C9 - O3	1.29(1)	C24 - O6	1.25(1)
C9 - N3	1.34(1)	C24 - N6	1.36(1)
N3 - C10	1.40(2)	N6 - C25	1.41(2)
C10 - C11	1.39(2)	C25 - C26	1.38(2)
C10 - C15	1.37(2)	C25 - C30	1.32(1)
C11 - C12	1.37(2)	C26 - C27	1.38(2)
C12 - C13	1.35(2)	C27 - C28	1.38(2)
C13 - C14	1.42(2)	C28 - C29	1.40(2)
C14 - C15	1.39(2)	C29 - C30	1.32(2)

Molecule 1		Molecule 2	
C4 - N1 - C5	119(1)	C19 - N4 - C20	117(1)
C1 - N1 - C5	119(1)	C16 - N4 - C20	122(1)
C1 - N1 - C4	122(1)	C16 - N4 - C19	121(1)
N1 - C1 - C8	117(1)	N4 - C16 - C23	117(1)
N1 - C1 - N2	118(1)	N4 - C16 - N5	123(1)
N2 - C1 - C8	125(1)	N5 - C16 - C23	120(1)
C1 - N2 - C2	120(1)	C16 - N5 - C17	116(1)
N2 - C2 - C3	126(1)	N5 - C17 - C18	125(1)
N2 - C2 - O1	114(1)	N5 - C17 - O4	113(1)
O1 - C2 - C3	120(1)	O4 - C17 - C18	122(1)
C2 - O1 - H1	103(6)	C17 - O4 - H3	107(5)
C2 - C3 - C9	121(1)	C17 - C18 - C24	118(1)
C2 - C3 - C4	119(1)	C17 - C18 - C19	120(1)
C4 - C3 - C9	121(1)	C19 - C18 - C24	122(1)
N1 - C4 - C3	116(1)	N4 - C19 - C18	114(1)
C3 - C4 - O2	131(1)	C18 - C19 - O5	129(1)
N1 - C4 - O2	114(1)	N4 - C19 - O5	117(1)
N1 - C5 - C6	121(1)	N4 - C20 - C21	121(1)
C5 - C6 - C7	121(1)	C20 - C21 - C22	117(1)
C6 - C7 - C8	116(1)	C21 - C22 - C23	123(1)
C1 - C8 - C7	127(1)	C16 - C23 - C22	120(1)
C3 - C9 - N3	121(1)	C18 - C24 - N6	117(1)
C3 - C9 - O3	120(1)	C18 - C24 - O6	122(1)
O3 - C9 - N3	119(1)	O6 - C24 - N6	121(1)
C9 - N3 - C10	131(1)	C24 - N6 - C25	130(1)
N3 - C10 - C15	117(1)	N6 - C25 - C30	115(1)
N3 - C10 - C11	123(1)	N6 - C25 - C26	123(1)
C11 - C10 - C15	120(1)	C26 - C25 - C30	121(1)
C10 - C11 - C12	116(1)	C25 - C26 - C27	118(1)
C11 - C12 - C13	126(1)	C26 - C27 - C28	122(1)
C12 - C13 - C14	120(1)	C27 - C28 - C29	116(1)
C13 - C14 - C15	114(1)	C28 - C29 - C30	122(1)
C10 - C15 - C14	125(1)	C25 - C30 - C29	121(1)

amide nitrogen is detected. The structure of compound **3a** was confirmed by X-ray analysis. The crystal structure of **3a** consists of $C_{15}H_{11}N_3O_3$ molecules and of chloroform solvent molecules in a 2:1 ratio. In the unit cell there are two crystallographically independent $C_{15}H_{11}N_3O_3$ molecules, whose geometries appear to be substantially identical. Both molecules show two strong intramolecular hydrogen bonds between the amide moiety and the pyrimidine

Table 2

Positional Parameters ($x10^4$) and Equivalent or Isotropic Thermal Parameters ($x10^3$)

Atom	x/a	y/b	z/c	U
N1	-3839(15)	2538(3)	9750(5)	64(3)
C1	-5552(21)	2913(5)	9870(7)	76(4)
N2	-7457(16)	2944(4)	9434(6)	72(4)
C2	-7689(22)	2639(5)	8923(8)	80(5)
O1	-9670(15)	2708(3)	8517(5)	91(3)
C3	-6101(18)	2253(4)	8774(7)	52(4)
C4	-4149(19)	2185(4)	9193(7)	61(4)
O2	-2515(11)	1873(3)	9175(4)	71(2)
C5	-1847(18)	2503(4)	10195(6)	74(4)
C6	-1491(19)	2822(4)	10721(7)	82(4)
C7	-3226(20)	3202(4)	10851(7)	93(5)
C8	-5086(21)	3223(4)	10404(7)	82(5)
C9	-6579(20)	1933(4)	8192(7)	68(4)
O3	-8482(13)	1992(3)	7805(4)	77(3)
N3	-5058(15)	1573(3)	8044(5)	58(3)
C10	-5103(19)	1226(4)	7512(7)	60(4)
C11	-7039(20)	1151(4)	7056(6)	80(4)
C12	-6799(20)	791(4)	6569(7)	85(4)
C13	-4899(19)	500(4)	6515(7)	81(4)
C14	-2913(19)	567(4)	6980(6)	77(4)
C15	-3164(18)	933(4)	7470(7)	67(4)
N4	5880(14)	138(3)	9018(5)	50(3)
C16	4046(19)	115(4)	8526(7)	56(4)
N5	2204(14)	423(3)	8508(5)	60(3)
C17	2207(19)	761(4)	9005(7)	58(4)
O4	340(12)	1067(3)	8954(5)	67(3)
C18	3989(16)	817(4)	9523(6)	43(3)
C19	5878(17)	493(4)	9569(7)	51(3)
O5	7534(11)	468(2)	10015(4)	63(2)
C20	7759(19)	-182(4)	9016(6)	70(4)
C21	7877(18)	-546(4)	8527(7)	69(4)
C22	6014(19)	-569(4)	8028(6)	78(4)
C23	4198(18)	-260(4)	8012(6)	65(4)
C24	3711(19)	1216(4)	10036(7)	61(4)
O6	1967(13)	1504(3)	10009(5)	72(3)
N6	5489(14)	1272(3)	10524(5)	56(3)
C25	5666(19)	1589(4)	11092(7)	60(4)
C26	3893(19)	1900(4)	11257(7)	70(4)
C27	4272(19)	2189(4)	11833(7)	81(4)
C28	6311(20)	2153(4)	12250(7)	97(5)
C29	8007(22)	1831(4)	12032(7)	99(5)
C30	7653(16)	1562(4)	11474(6)	45(3)
C11	6444(7)	1144(2)	3803(3)	179(5)
C12	10515(6)	768(2)	3416(3)	172(3)
C13	9686(11)	663(2)	4727(3)	275(7)
C31	9265(21)	1022(5)	4094(8)	101(5)
H1	-0.965(18)	0.242(5)	0.820(6)	105(24)
H3	0.050(15)	0.133(4)	0.942(6)	216(31)

group which confer on the molecules a quasi-planar arrangement (H1··O3 = 1.57(12), H2··O2 = 1.83(1), H3··O6 = 1.46(10), H4··O5 = 1.78(1) Å). Besides two intermolecular hydrogen bonds exist between the two independent molecules (H3··O2 = 2.25(9), H2··O4 = 2.69(1) Å). Figure 1 reports the structure of the two independent molecules interacting through these hydrogen bonds. Bond distances and angles are reported in Table 1.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Büchi 512 apparatus. Infrared spectra were recorded as potassium bromide pellets using a Perkin-Elmer 881 Infrared spectrophotometer. Proton nmr spectra were determined on a Varian Gemini 200 spectrometer. Elemental analyses for C, H and N were performed using Perkin-Elmer 240 C Elemental Analyzer. The molecular structure was determined by the X-ray diffraction using an Enraf-Nonius CAD4 automatic diffractometer.

Heterocyclic amines **1**, **4**, and **6** are commercially available, 2-substituted ethyl 2,5-dihydro-5-oxoisoxazole-4-carboxylates **2a,b** were prepared according to the literature procedure [3].

General Procedure for the Reaction of 2-Aminopyridine (**1**) with Isoxazoles **2a,b**.

A small flask containing a mixture of 0.19 g (0.002 mole) of 2-aminopyridine (**1**) and ethyl 2,5-dihydro-5-oxo-2-arylisoxazole-4-carboxylate (**2**) (0.002 mole) was poured for 2 minutes in an oil bath preheated at 200°. The reaction mixture was allowed to cool and then stirred with a little ethanol and filtered. The collected solid was recrystallized from a suitable solvent.

N-Phenyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**3a**).

This compound was obtained in 35% yield, mp 219-220° from dimethylformamide; ir: ν CO 1674 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.06-9.06 (m, 9H, phenyl and pyridine protons), 11.48 (s, 1H, NH), 15.87 (s, 1H, OH).

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.06; H, 3.94; N, 14.94. Found: C, 64.20; H, 3.80; N, 15.01.

N-(4-Methylphenyl)-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**3b**).

This compound was obtained in 37% yield, mp 268-269° from dimethylformamide; ir: ν CO 1667 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (s, 3H, CH_3), 7.17-9.02 (m, 8H, phenyl and pyridine protons), 11.55 (s, 1H, NH), 15.75 (s, 1H, OH).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.01; H, 4.63; N, 14.36.

General Procedure for the Reaction of Amines **4,6** with Isoxazoles **2a,b**.

A small flask containing a mixture of **4** or **6** (0.002 mole) and ethyl 2,5-dihydro-5-oxo-2-arylisoxazole-4-carboxylate (**2**) (0.002 mole) was poured in an oil bath preheated at 190°. When all the solid mixture was molten the flask was quickly removed and allowed to cool. The reaction mixture was stirred with a little ethanol and filtered. The collected solid was recrystallized from a suitable solvent.

N-Phenyl-7-hydroxy-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (**5a**).

This compound was obtained in 24% yield, mp 317-318° from dimethylformamide-ethanol; ir: ν CO 1666 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.16-8.08 (m, 7H, phenyl and thiazole protons), 11.48 (s, 1H, NH), 15.76 (s, 1H, OH).

Anal. Calcd. for $C_{13}H_9N_3O_3S$: C, 54.35; H, 3.16; N, 14.63. Found: C, 54.40; H, 3.06; N, 14.78.

N-(4-Methylphenyl)-7-hydroxy-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (**5b**).

This compound was obtained in 22% yield, mp 273-274° from dimethylformamide; ir: ν CO 1668 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.19-8.11 (m, 6H, phenyl and thiazole protons), 11.47 (s, 1H, NH), 15.74 (s, 1H, OH).

Anal. Calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.81; H, 3.68; N, 13.95. Found: C, 55.92; H, 3.71; N, 13.72.

N-Phenyl-2-hydroxy-4-oxo-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxamide (**7a**).

This compound was obtained in 45% yield, mp 321-322° from dimethylformamide-ethanol; ir: ν CO 1667 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.19-9.07 (m, 9H, phenyl and benzothiazole protons), 11.55 (s, 1H, NH), 16.45 (s, 1H, OH).

Anal. Calcd. for $C_{17}H_{11}N_3O_3S$: C, 60.53; H, 3.29; N, 12.46. Found: C, 60.29; H, 3.20; N, 12.55.

N-(4-Methylphenyl)-2-hydroxy-4-oxo-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxamide (**7b**).

This compound was obtained in 40% yield, mp 313-314° from dimethylformamide; ir: ν CO 1671 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 7.20-8.97 (m, 8H, phenyl and benzothiazole protons), 11.56 (s, 1H, NH), 16.12 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96. Found: C, 61.62; H, 3.79; N, 11.72.

X-ray Crystallographic Data of **3a**.

Crystals of $C_{15}H_{11}N_3O_3$ 0.5$CHCl_3$ were obtained from chloroform. A single crystal of appropriate size (0.6 x 0.4 x 0.3 mm) was employed. Determination of the cell parameters was performed by least-squares refinement of 25 reflections. The compound crystallizes in the monoclinic system, space group $P2_1/c$ with a = 5.843(1), b = 25.648(5), c = 20.372(2) Å, β = 96.94(1)°; Z = 8; V = 3030.6(8) $Å^3$; μ = 3.50 cm^{-1}; Dc = 1.37 g cm^{-3}; 4486 reflections were collected in the range $5 < 2\theta < 124°$, using Cu-Kα radiation (λ = 1.5418 Å), θ-2θ scan mode. The structure was solved by direct methods of SIR88 [4] and refined by full-matrix least-squares to R = 0.107 and Rw = 0.075 ($w = 1/\sigma^2$), by using the 1767 observed reflections having $I > 3\sigma(I)$ for 210 parameters refined. The chlorine atoms of the chloroform were refined anisotropically, whereas the other atoms were considered thermally isotropic. The positions of the four hydrogen atoms involved in the strong hydrogen bonds, *i.e.* H1, H2, H3, and H4, well appeared in a ΔF Fourier map. The hydrogen atoms were refined in fixed positions, except those of the two OH groups which were individuallyl refined. The fractional atomic coordinates and equivalent isotropic parameters for the individually refined atoms are reported in Table 2. Further data are available on request from the authors.

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